IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	:	Walker et al.
Serial No.	:	10/080,876
Filed	:	February 22, 2003
For	:	REGULATION OF INTRACELLULAR GLUCOCORTICOID CONCENTRATION
Examiner	:	Theodore J. Criares
Group Art Unit	:	1617

745 Fifth Avenue, New York, NY 10151

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

DECLARATION OF BRIAN R. WALKER AND JONATHAN R. SECKL

WE, BRIAN R. WALKER AND JONATHAN R. SECKL, declare and state that:

1. We are the named inventors on the above-captioned application ("the present application") and are familiar with it and its prosecution, including the claims, and the November 19, 2003 Office Action. It is our understanding that the pending claims read as follows:

> --14. A method for reducing circulating fatty acids from, or maintained by, reductase activity of 11-Beta-hydroxysteroid dehydrogenase 1 (11-Beta HSD1) in adipose tissue in a patient in need thereof comprising
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> determining reductase activity of 11 Beta HSD1 in adipose tissue, and
>
> inhibiting said reductase activity of 11-Beta HSD1 in adipose tissue in said patient.
>
> 15. A method for reducing circulating fatty acids from, or maintained by, reductase activity of 11-Beta-hydroxysteroid dehydrogenase 1 (11-Beta HSD1) in adipose tissue in a patient in need thereof comprising
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> determining reductase activity of 11 Beta HSD1 in adipose

tissue,

determining whether a compound or composition inhibits said reductase activity of 11 Beta HSD1 in adipose tissue, and

administering to said patient said compound or composition which inhibits said reductase activity of 11-Beta HSD1 in adipose tissue, in an amount effective to so inhibit said reductase activity of 11-Beta HSD1 in adipose tissue.

16. The method of claim 14 wherein the inhibiting is by administering carbenoxolone or a pharmaceutically acceptable salt thereof.

17. The method of claim 15, wherein determining whether a compound or composition inhibits said reductase activity of 11-Beta HSD1 in adipose tissue comprises:

obtaining reductase activity of 11-Beta HSD1 in an isolated *in vitro* adipocyte cell population, and

contacting said compound or composition with said adipocyte cell population.

18. The method of claim 15 wherein the compound or composition which inhibits said reductase activity of 11-Beta HSD1 in adipose tissue is carbenoxolone or a pharmaceutically acceptable salt thereof.

19. The method of claim 14, wherein said patient suffers from one of the following: obesity, insulin resistance, or obesity and insulin resistance.

20. The method of claim 15, wherein said patient suffers from one of the following: obesity, insulin resistance, or obesity and insulin resistance.

21. A method for treating obesity, insulin resistance, or obesity and insulin resistance by regulating reductase activity of 11-Beta-hydroxysteroid dehydrogenase 1 (11-Beta HSD1) in adipose tissue in a patient in need thereof comprising

determining reductase activity of 11 Beta HSD1 in adipose tissue, and

inhibiting said reductase activity of 11-Beta HSD1 in adipose tissue in said patient.

22. A for treating obesity, insulin resistance, or obesity and insulin resistance by regulating reductase activity of 11-Beta-hydroxysteroid dehydrogenase 1 (11-Beta HSD1) in adipose tissue in a patient in need thereof comprising

determining reductase activity of 11 Beta HSD1 in adipose tissue,

determining whether a compound or composition inhibits said reductase activity of 11 Beta HSD1 in adipose tissue, and

administering to said patient said compound or composition which inhibits said reductase activity of 11-Beta HSD1 in adipose tissue, in an amount effective to so inhibit said reductase activity of 11-Beta HSD1 in adipose tissue.--

2. More in particular, we are advised and therefore believe that in the November 19, 2003 Office Action, these claims were rejected under 35 U.S.C. §112 because the Examiner questions "compounds which inhibit the reductase activity of 11-Beta-hydroxysteroid dehydrogenase I in adipose tissue" and enablement for such inhibitors beyond carbenoxolone.

3. We are also familiar with the present application and the concurrently-filed Communication forwarding Declaration, and that the arguments in that Communication are based on our assertions herein.

4. Furthermore we, Professor Jonathan R Seckl and Dr Brian R Walker, respectfully submit that we are experts in the field of 11β-hydroxysteroid dehydrogenases. Brief *curricula vitae* are attached as Appendices A and B. We have both been active researchers in this field for more than 10 years and, together and separately, have published more than 200 relevant primary articles in peer-reviewed journals and more than 80 review articles and contributions to books. We have obtained very substantial external research funding for our work in this area in open competition. We both lead research groups within the University of Edinburgh in which we

supervise more than 40 full-time research staff who are investigating aspects of glucocorticoid biology, including 11β-hydroxysteroid dehydrogenases. We are both asked regularly to speak to the subject of 11β-hydroxysteroid dehydrogenase biology at national and international scientific meetings.

5. Accordingly, in view of our education, training and experience, we are considered by our peers to be experts in the field to which the present application pertains, and qualified to knowledgeably characterize the art to which the invention in the present application relates, and to speak as to the present application, and the invention claimed, including being qualified to present expert opinions about the present invention and literature in support of it, and documents cited against the present invention. Moreover, we respectfully submit that we are qualifed to state the knowledge in the art, and that which the skilled artisan would not have required any undue experimentation to practice, e.g., the enablement and the written description in the present application, and what the skilled artisan would have been taught, as well as what would have been obvious and nonobvious to the skilled artisan.

6. Thus, this Declaration is intended to assert the sufficiency of the enablement of the claimed subject matter of the present application (as of original filing of the parent application in August 1995), i.e., to respond to the rejections of the present application under 35 U.S.C. §112, first paragraph; which rejections we respectfully request be reconsidered and withdrawn in view of this Declaration and the attachments hereto. All documents cited herein are listed on a reference list that appears before the closing paragraph and our signatures. All documents cited herein are incorporated herein by reference, and a copy of those documents indicated in the following text as attached is included with this Declaration, to assist the Examiner in confirming our assertions and discussions herein. The Examiner is respectfully requested to consider and make of record documents cited herein.

7. With respect to the rejections under Sections 112, initially it is noted that the Figures provide doses of an inhibitor of the reductase activity of 11-Beta HSD1 from which the skilled artisan can make and use the claimed invention, without undue experimentation. Additionally, as to inhibitors of 11-Beta HSD1, the attached article by Monder and White, in Table IV at pages 196-198 provides a rather lengthy list of inhibitors of 11β-hydroxysteroid dehyrogenase, such that contrary to the Office Action, the skilled artisan understands compounds that "inhibit the reductase activity of 11-Beta-hydroxysteroid dehydrogenase I" and would readily

understand how to use such compounds in the methods of the present invention without any undue experimentation.

8. Indeed, in addition to the lengthy list of inhibitors in Monder and White, we note that documents cited in the prosecution of the parent application, U.S. Application Serial Number 09/029,535, now U.S. Patent 6,368,816, also show inhibitors and modes of administration, such as Walker et al., "Carbenoxolone Increases Hepatic Insulin Sensitivity in Man: A Novel Role for 11-oxosteroid Reductase in Enhancing Glucocorticoid Receptor Activation," J. Clin. Endocrinology and Metabolism 80 (11): 3155-59 (1995). Thus, in the art, carbenoxolone and the lengthy list in Monder and White were known inhibitors. Gomez-Sanchez et al., "Central hypertensinogenic effects of glycyrrhizic acid and carbenoxolone," Am J Physiol 263 (6 Pt 1): E1125-E1130 (1992) showing that licorice, glycyrrhizic acid, and carbenoxolone were known inhibitors, as well as the infusion of glycyrrhizic acid and carbenoxolone into the lateral ventricle of the brain of the rat at doses less than that which has an effect when infused subcutaneously, produces hypertension, showing that such compounds were administered subcutaneously, orally, and by infusion; *see also* Whorwood et al., "Licorice inhibits 11 beta-hydroxysteroid dehydrogenase messenger ribonucleic acid levels and potentiates glucocorticoid hormone action," Endocrinology 132 (6): 2287-92 (1993) (copy of Abstract attached). Even further still, Homma et al., "A Novel 11β-Hydroxsteroid Dehydrogenase Inhibitor Contained in Saiboku-To, a Herbal Remedy for Steroid-dependent Bronchial Asthma," J. Pharm Pharmacol 46:305-309 (1994) (copy attached), Zhang et al., "Inhibition of 11β-Hydroxysteroid Dehydrogenase Obtained from Guinea Pig Kidney by Furosemide, Naringenin and Some Other Compounds," J Steroid Biochem Molec Biol 49(1):81-85 (1994) (copy attached), and Lee et al., "Grapefruit juice and its flavenoids inhibit 11β-hydroxysteroid dehydrogenase," Clin Pharmacol Ther 59:62-71 (1996) (copy attached), evince even more inhibitors that can be administered in known ways (both in terms of doses and routes of administration), such as flavenoids, which "are sold in tablet form in health food stores and drug stores," and herbs or constituents of herbs. *See also* Morris et al., "Endogenous 11 beta-hydroxysteroid dehydrogenase inhibitors and their role in glucocorticoid Na+ retention and hypertension," Endocr Res 22(4):793-801 (1996) (progesterone metabolites as inhibitors, and progesterone is also a substance that can be administered – both in terms of doses and routes of administration - without undue experimentation).

9. Furthermore, attached as Appendix C are two pages of a presentation originally provided to the Patent Office during the October 2, 2001 Interview during the prosecution of U.S. Application Serial Number 09/029,535, now U.S. Patent 6,521,267, and which was provided to the present Examiner during the March 10, 2004 Interview. Appendix C depicts results obtained with various known compounds, including chenodeoxycholic acid and frusemide in addition to carbenoxolone, that inhibit 11B-reductase in intact primary neurons and adipocytes. Therefore, Appendix C provides additional known inhibitors that so inhibit the enzyme in amounts disclosed in the application, such that based upon the knowledge in the art and the disclosure in the application, the invention can be practiced by one of skill in the art without undue experimentation.

10. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the Section 112 rejections: The present application contains both a written description and enablement for the claimed methods, and, one skilled in the art, from the knowledge in the art and the teachings in the application, can practice the claimed methods, without any undue experimentation, including without any undue experimentation in selecting a suitable inhibitor, and a dose therefore and a route of administration thereof.[a]

SUMMARY AND REQUEST FOR INTERVIEW

11. This declaration shows that the claimed subject matter is sufficiently described and enabled in the present application, and can be practiced without any undue experimentation. Accordingly, it is respectfully requested that the rejections of the November 19, 2003 Office Action be reconsidered and withdrawn. Moreover, we would welcome the opportunity to further explain any aspect of the present invention or this declaration to the Examiner, her SPE, and a Group 1600 Practice Specialist, in person. Therefore, if any issue remains as an impediment to allowance, we respectfully request a personal interview with the Examiner, his SPE, and a Group 1600 Practice Specialist, prior to issuance of any paper other than a Notice of Allowance; and, pursuant to this request the Examiner is also asked if he could please contact our representative, Mr. Thomas J. Kowalski, FROMMER LAWRENCE & HAUG LLP, 745 Fifth Avenue, New

[a] In this regard, we are advised and therefore believe that a specification need only begin teaching where the prior art leaves off. Thus, the present application did not need to provide an exhaustive list in inhibitors, doses of inhibitors, and routes of administration.

York, NY 10151, tel: 212-588-0800, fax: 212-588-0500, email: tkowalski@flhlaw.com, to arrange a mutually convenient time and manner for such an interview.

REFERENCES

12. References cited in this Declaration, and incorporated herein by reference, as shown in Appendix D, include:

Gomez-Sanchez et al., "Central hypertensinogenic effects of glycyrrhizic acid and carbenoxolone," **Am J Physiol** 263 (6 Pt 1): E1125-E1130 (1992).

Homma et al., "A Novel 11β-Hydroxsteroid Dehydrogenase Inhibitor Contained in Saiboku-To, a Herbal Remedy for Steroid-dependent Bronchial Asthma," **J. Pharm Pharmacol** 46:305-309 (1994).

Lee et al., "Grapefruit juice and its flavenoids inhibit 11β-hydroxysteroid dehydrogenase," **Clin Pharmacol Ther** 59:62-71 (1996).

Monder C, White PC. 11β-Hydroxysteroid dehydrogenase. **Vitamins and Hormones** 47: 187-271 (1993).

Morris et al., "Endogenous 11 beta-hydroxysteroid dehydrogenase inhibitors and their role in glucocorticoid Na+ retention and hypertension," **Endocr Res** 22(4):793-801 (1996).

Walker BR, Connacher AA, Lindsay RM, Webb DJ, Edwards CRW. Carbenoxolone increases hepatic insulin sensitivity in man: a novel role for 11-oxosteroid reductase in enhancing glucocorticoid receptor activation. **J.Clin.Endocrinol.Metab.** 80: 3155-3159 (1995).

Whorwood et al., "Licorice inhibits 11 beta-hydroxysteroid dehydrogenase messenger ribonucleic acid levels and potentiates glucocorticoid hormone action," **Endocrinology** 132 (6): 2287-92 (1993) (Abstract).

Zhang et al., "Inhibition of 11β-Hydroxysteroid Dehydrogenase Obtained from Guinea Pig Kidney by Furosemide, Naringenin and Some Other Compounds," **J Steroid Biochem Molec Biol** 49(1):81-85 (1994).

13. We further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Dated:_____ By:_____
Professor Jonathan R. Seckl

Dated:_____ By:_____
Dr. Brian R. Walker